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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/990,427 | 11/14/2001 | David Botstein | P2730P1C10 | 4110 |

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| EXAMINER | |
|---|---|
| CHERNYSHEV, OLGA N | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1649 | |

DATE MAILED: 09/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/990,427 | BOTSTEIN ET AL. | |
| | Examiner | Art Unit | |
| | Olga N. Chernyshev | 1649 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *119-123* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/17/6*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 17, 2006 has been entered.

2. Claims 119-123 are pending in the instant application. Claims 119-123 are under examination in the instant office action.

3. The Text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

5. Applicant's arguments filed on August 17, 2006 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

### *Claim Rejections - 35 USC § 101*

6. Claims 119-123 stand rejected under 35 U.S.C. 101 because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility for those reasons of record as specifically articulated in the previous communications from the office. Briefly, the instant application has provided a description of an isolated DNA encoding a protein and the protein encoded thereby. The instant application does not disclose a specific

biological role for this protein or the antibody that binds to this protein or their significance to a particular disease, disorder or physiological process, which one would wish to manipulate for a desired clinical effect.

At pages 4-13 of the Response, Applicant presents analysis of publications pertained to the issue of correlation of mRNA levels and corresponding protein levels. Specifically, Applicant submits that, "it is more likely that a person of ordinary skill in the pertinent art would recognize such a positive correlation between gene amplification levels and protein levels" (page 4 of the Response). Applicant argues that, " a correlation between gene (DNA) amplification and elevated protein levels exists, in general". Applicant further refers to the second Declaration of Dr. Polakis and to Declaration of Scott to support the argument that elevated mRNA levels correlate with higher values of the corresponding protein. Applicant's arguments have been fully considered but are not persuasive for the following reasons.

The Examiner maintains the position that the instant claimed antibodies that bind PRO830 polypeptides lack specific, substantial and credible utility and are not enabled as cancer markers or as future therapeutic agents/targets because the instant specification, as filed, fails to provide any evidence or sound scientific reasoning to support a conclusion that the instant PRO830 polypeptides are specifically associated with lung cancer. The instant specification discloses that the gene (DNA) encoding claimed PRO830 polypeptide was found to be amplified 1.13 to 1.35-fold in five out of fourteen samples of lung cancer as compared to corresponding pooled DNA levels in blood of healthy subjects (Table at p.550 of the instants specification). The disclosure fails to provide any information regarding the samples of cancerous tissue, such as size, number, cancer type, protocol of obtaining etc. There appears to be also no explanation

presented in the instant specification as why one skilled in the art would consider a DNA, which is slightly amplified in 35% of samples of cancerous lung tissue and not changed in 65% of cases, be useful as a marker for lung cancer. Based on the information provided, one would reasonably conclude that the instant disclosed DNA could not possibly serve as a cancer marker because it would more likely than not (65% as compared to 35% cases) fail to identify lung cancer cells. Furthermore, in view of the art recognition that levels of DNA are not always predictable of encoding protein levels (see reasons of record in the previous office action of record), no extrapolation can be made from what appears to be non-significant (35% accuracy) gene amplification data to differential distribution of the claimed PRO830 polypeptides in lung cancer. Thus, because the instant specification, as filed, fails to disclose if the PRO830 polypeptides are differentially expressed in lung cancer, one would have reasons to conclude that the instant anti-PRO830 antibodies are not useful for diagnosis of lung cancer and further that the instant invention was not completed as filed, and, therefore, clearly lacks utility in currently available form.

The asserted utility of the claimed anti-PRO830 antibodies is to use the instant molecules as lung cancer markers. The instant specification discloses that PRO830 DNA was amplified 1.13-1.35-fold in 35% of limited number of samples (total fourteen) of lung cancer. However, there is no disclosure as what the levels of PRO830 overexpression are. If a clinician took a lung tissue sample from a patient with suspected lung cancer, what is the likelihood that when compared with normal tissue, the level of an antibody that binds to a polypeptide of SEQ ID NO: 175 from the patient would be higher? How many samples would be needed? What sensitivity would be needed? Would the normal tissue have to be a pooled sample or could it be from a

single individual? Applicant has provided no indication of the nature or number of samples that were used. The only thing Applicant teaches is that the gene (DNA) was slightly amplified in less than half samples examined, and this does not enable the skilled artisan to differentiate amongst expression levels in order to diagnose any diseases. Without clear explanation as to the significance of finding of slight DNA amplification in few cancer samples, or more specifics about necessary sample size, expression level range for normal and tumor tissues, types of lung tumor tissue that can be used, the specification has not provided the invention in a form readily usable by the skilled artisan such that significant further experimentation is unnecessary.

At page 12 of the Response, Applicant states that total of 148 references have been submitted with the Response to support Applicant's assertion that changes in mRNA level generally lead to corresponding changes in the level of the expressed protein. Applicant's arguments have been carefully considered but are not persuasive for the following reasons. The validity, importance and quantity of the publications presented and discussed by Applicant are not disputed. However, first, the strong opposing evidence that exists on a topic of predicting protein expression from corresponding mRNA levels also has to be taken in consideration. For example, in article by Anderson et al. (Electrophoresis, 1997, Vol. 18, pp.533-7) the authors investigated overall level of correlation between the mRNA and protein abundances. The authors report that the correlation coefficient obtained from comparison of mRNA and protein levels was 0.48, "[t]his number is intriguingly close to the middle position between a perfect correlation (1.0) and no correlation whatever (0.0). One simple interpretation of such a value is that the two major phases of gene expression regulation (transcription through message degradation on the one hand, and translation through protein degradation on the other) are of approximately equal

importance in determining the net output of functional gene product (protein)" (p.536, middle at first column). Second, Applicant's arguments regarding correlation between mRNA levels and protein levels appear to be lacking importance in the instant case as the instant specification discloses data pertained to DNA amplification and not mRNA measurement. Regarding the merit of the argument, even if DNA levels were fully corresponding to encoded protein levels, the issue at hand would still remain as how to use these claimed molecules, the anti- PRO830 antibodies, in diagnosis of lung cancer if there is no clear disclosed correlation between the change in level of PRO830 polypeptide and lung cancer.

The Second Declaration of Polakis under 37 CFR 1.132 filed on August 03, 2006 is insufficient to overcome the rejection of claims 119-123 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action for the following reasons.

In assessing the weight to be given to expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See *Ex parte Simpson*, 61 USPQ2d 1009 (BPAI 2001), *Cf. Redac Int'l. Ltd. v. Lotus Development Corp.*, 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), *Paragon Podiatry Lab., Inc. v. KLM Lab., Inc.*, 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993).

Affidavits or declarations are provided as evidence and must set forth facts, not merely conclusions. *In re Pike and Morris*, 84 USPQ 235 (CCPA 1949).

The Second Polakis declaration has been fully considered to the following effect:

In the instant case, the nature of the fact sought to be established is whether or not the increased mRNA levels are predictive of the increased protein levels. (1) Dr. Polakis declares that 28 of 31genes identified as being detectably overexpressed at the mRNA level were found also to have increased protein levels. Dr. Polakis submits that "it is my considered scientific opinion that for human genes, as increased level of mRNA in tumor tissue relative to a normal tissue more often than not correlates to a similar increase in abundance of the encoded protein in the tumor tissue relative to the normal tissue" (section 6 of the Declaration). (2) It is important to note that the instant specification only discloses that PRO-encoding nucleic acids were amplified (page 550 of the specification), and does not disclose any information regarding mRNA levels or microarray technology. (3) The Declaration presents references to facts; however, there is no indication of *how much* the mRNA and protein were overexpressed, as there is no actual description of the experiments that were done, but rather a conclusory statement as to what was measured, and what it means. Furthermore, there is an opposing evidence in the literature showing that mRNA levels are not always predictive of protein expression, such evidence that cannot be ignored or discarded, see discussion earlier in this office action. (4) Finally, regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee.

The Declaration of Scott under 37 CFR 1.132 filed on August 17, 2006 is insufficient to overcome the rejection of claims 119-123 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action for the following reasons. Similarly to the Declarations of Polakis, the instant filed Declaration presents support for validity and predictability of DNA microarray technique, wherein in the instant application fluorometric DNA quantitation using

Hochst dye and TaqMan assay were used (p.548-549 of the specification). Also, regarding the interest of the expert in the outcome of the case, it is noted that Dr. Scott is directely affiliated with the assignee.

The Examiner maintains the position that because the instant specification fails to present any information regarding any specific values for the levels of overexpression of PRO830 polypeptides, then a substantial amount of further research would be necessary to establish or reasonably confirm if PRO830 polypeptides are differentially expressed in lung cancer and, consequently, if anti-PRO830 antibodies could be used as markers for this types of cancer, as asserted by Applicant.

§101 requires a utility that is "substantial", i.e., one that provides a specific benefit in currently available form, *Brenner*, 383, U.S. at 534-35, 148 USPQ at 695. *Brenner's* standard has been interpreted to mean that "vague, general disclosures or arguments of "useful in research" or "useful as building blocks of value to the researcher" would not satisfy §101. See *Kirk*, 376 F. 2d at 945 153 USPQ at 55 (interpreting *Brenner*). In the instant case, the record does not support Applicant's position that characterization of a polypeptide as being encoded by a nucleic acid, which appears to be slightly amplified in 35% of samples of lung cancer tissue, would have suggested a specific and substantial basis for patentable utility of the antibodies that bind to that polypeptide as lung cancer markers, to a person skilled in the art at the time the application was filed. In the terms used by the *Brenner* Court, such a characterization does not provide a specific utility in currently available form.

Applicant claims a product asserted to be useful in marking lung cancer but the specification does not disclose how to interpret those data. Just as the process claimed in *Brenner*

lacked utility because the specification did not disclose how to use the end-product, the product claims here lack utility, based on their use, e.g. markers for lung cancer, because the specification does not disclose how to use the SEQ ID NO: 175-specfic gene expression with respect to the claimed antibody molecules.

Applicant discloses that PRO830 DNA is amplified 1.13 to 1.35-fold in 35% of lung cancer tissue samples as compared to the pooled samples of DNA from blood of healthy control subjects; however, there is no disclosure how to extrapolate these data into the use of anti-PRO830 antibodies as lung cancer markers. One skilled in the art readily understands that in order to use the antibodies as a marker for lung tumors, a skilled practitioner would have to resort to a significant amount of further research to experiment and discover at least if PRO830 polypeptide itself is expressed in altered levels or forms in lung cancer.

Applicant's asserted utility for the antibodies that bind PRO830 polypeptide of SEQ ID NO: 175, particularly in view of a lack of knowledge as to the biological function of the PRO830 polypeptide, the type of tumor which can be diagnosed, and how much of the polypeptide of SEQ ID NO: 175 is indicative of disease, constitutes a utility that requires further research to identify or reasonably confirm "real world" context of use. There is little doubt that, after complete characterization, this protein of SEQ ID NO: 175 and antibodies that bind to it may be found to have a specific and substantial credible utility. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. See *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966). In the instant case the claimed antibodies appear to be suitable only for further research.

Thus, for reasons of record fully explained in the previous communication of record and reasons above, the instant rejection is maintained.

***Claim Rejections - 35 USC § 112***

7. Claims 119-123 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a clear asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

***Conclusion***

8. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (571) 272-0870. The examiner can normally be reached on 8:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR

system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Olga N. Chernyshev, Ph.D.
Primary Examiner
Art Unit 1649

September 18, 2006